



Aging, Immunity, and Neuroinflammation: The Modulatory Potential of Nutrition

Svetlana Di Benedetto and Ludmila Müller

Contents

Introduction	301
Immunosenescence and Inflammaging	303
Neuroinflammation and the Aging Brain	308
The Impact of Nutrition and Physical Activity	310
Conclusions	316
References	317

Key Points

- The changes in the immune system that accompany human aging are very complex and are generally referred to as immunosenescence.
- The process of aging is commonly accompanied by low-grade inflammation thought to contribute to neuroinflammation and to many age-related diseases.
- Several lifestyle strategies, such as intervening to provide an adequate diet and physical and mental activity, have been shown to result in improved immune and neuroprotective functions, a decrease in oxidative stress and inflammation, and a potential increase in individual longevity.

Introduction

It is now clear that a variety of genetic and environmental factors impact upon health in old age, including effects on immunity. However, the relative contribution of these factors to immunosenescence will have to be more accurately established. These variables clearly include nutrition (micro and macro), physical activity, mental well-being, as well as gender and ethnicity, genetic background, psychosocial parameters (including stress), socioeconomic status, early-life events, and different chronic infections [1, 2].

Aging represents a major nutritional challenge, not only concerning the dietary supply of certain nutrients but also in terms of their altered metabolism [3]. Macro- and micronutrient deficiencies, which are very common in the elderly, have been found to be associated with a physiological decline in various body functions, which can lead to higher morbidity and mortality [2]. Nutrient status represents an important factor

S. Di Benedetto · L. Müller (✉)
Max Planck Institute for Human Development,
Berlin, Germany
e-mail: lmuller@mpib-berlin.mpg.de

contributing to immune competence, since undernutrition impairs the immune system, suppressing immune functions that are fundamental to host protection. Undernutrition leading to an impairment of immune function can be due either to insufficient intake of energy and macronutrients or to specific deficiencies in some particular micronutrients, although often these occur in combination [4].

Among other micronutrients, zinc, for instance, has an essential significance to health; its deficiency is responsible for various diseases. Zinc is one of the most important trace elements in the organism, with three major biological roles, as a catalyst, structural, and regulatory ion. It plays a critical role in organism homeostasis, in immune function, in oxidative stress, in apoptosis, and in other physiological activities [2, 5]. Thus, zinc deficiency may adversely affect the immunological status, increase oxidative stress, lead to the generation of inflammatory cytokines, and influence the progression of many chronic diseases, including atherosclerosis, neurological disorders, autoimmune diseases, age-related degenerative diseases, and various malignancies [5]. Zinc deficiency is known to decrease innate immune function. It particularly impairs the lytic activity of natural killer (NK) cells, reduces natural killer T (NKT)-cell cytotoxicity and immune signaling, influences the neuroendocrine-immune pathway, and alters cytokine generation in mast cells [6, 7].

However, excessive amounts of some nutrients may also impair immune function. Overnutrition, combined with an inactive lifestyle and sedentary behavior, promotes the accumulation of visceral fat and leads to obesity. Accumulating evidence indicates that obesity causes chronic low-grade inflammation and the development of systemic metabolic dysfunction that appears to be aetiologically associated with obesity-linked disorders [2, 8]. Adipose tissue acts as a key endocrine organ by releasing bioactive substances, known as adipokines, that may have either pro- or anti-inflammatory activities [9]. The production of pro-inflammatory adipokines, such as tumor necrosis factor (TNF), leptin, retinol-binding protein 4, lipocalin 2, IL-6,

IL-18, and angiopoietin-like protein 2, in expanding fat tissue increases, while the concentrations of anti-inflammatory cytokines are reduced [9]. This process is accompanied by an infiltration of adipose tissue with pro-inflammatory mediators and the induction of a low-grade inflammatory state, which is characterized by elevated levels of circulating inflammation markers, such as IL-6, TNF, and C-reactive protein (CRP). Adipose tissue is infiltrated with macrophages in two separate polarization states: M1, which produces pro-inflammatory cytokines, and M2, which produces anti-inflammatory cytokines. Therefore, it has been proposed that in the adipose tissue, a phenotypic switch takes place toward the macrophages of M1-phenotype, promoting the inflammatory state. This low-grade systemic inflammation is known to be associated with the development of atherosclerosis, neurodegeneration, insulin resistance, and the promotion of tumor growth [10]. It was also demonstrated that diet-induced obesity recruits monocytes from the periphery to the brain following herpes simplex virus (HSV)-1 latency in mice [11], leading to an exaggerated neuroinflammatory response and the promotion of neurodegeneration. While these phenomena are not limited to the elderly, they often tend to be exacerbated in older people who, for one reason or another, exercise less than the young [2].

Thus, many chronic and neurodegenerative diseases can be prevented by changing lifestyle and behavioral habits, particularly dietary habits, and exercise. For example, a positive effect of a 3-month regimen of comprehensive lifestyle changes (plant-based diet, moderate exercise, stress management, and improved social support) on increased telomerase activity was demonstrated in men with low-risk prostate cancer. After a 5-year follow-up, relative telomere lengths of lymphocytes were increased in the lifestyle intervention group and decreased in the control group [12]. According to the findings of another study on more than 23,000 adults, a healthy lifestyle alone lowered the risk of developing chronic diseases with known inflammatory etiology by 78% [13]. Although such changes are thought to be beneficial, more investigations are

needed to confirm whether this is really the case, and the full biological implications remain to be determined in large RCTs [2, 14].

Thus, recent studies indicate the need for a more in-depth, holistic approach to determine the optimal nutritional and behavioral strategies that would maintain immune and other physiological systems in the elderly people. Superimposed on chronological age alone, the remodeling of immunity as a result of interactions with the environment over the life course is instrumental in shaping immune status in later life. In addition to interactions with pathogens, host microbiome and nutrition, exercise and stress, and many other extrinsic factors are crucial modulators of this immunosenescence process [2]. In the next sections, we briefly describe the observed age-related changes in the immune system and then outline the possible contribution of inflammaging and immunosenescence to neuroinflammation and finally discuss the modulatory potential of nutrition and active lifestyle thereon.

Immunosenescence and Inflammaging

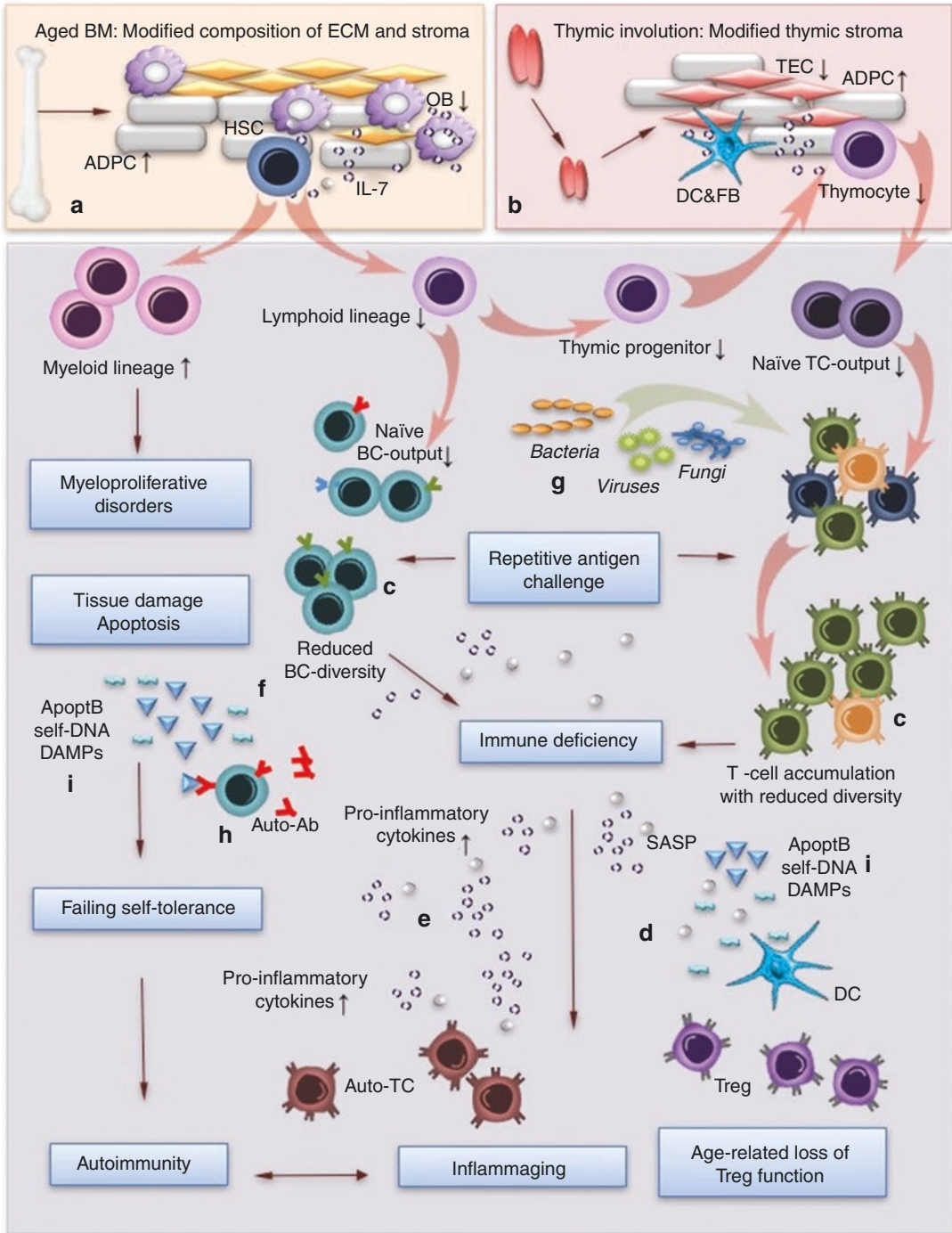
Human immune aging represents a universal and multifaceted process characterized by progressive immunodeficiency, chronic inflammation, and autoimmunity [15, 16]. The complex regulatory circuits required for maintaining appropriate physiological homeostasis may become compromised with aging [17, 18]. Age-related immune dysfunction (in combination with other mechanisms) may at least in part explain the process of aging itself [19], as originally proposed by Walford in 1969 [20].

In the course of aging, our immune system undergoes an imprecisely defined process of immunosenescence that affects both adaptive and innate immune systems. The most marked changes in adaptive immunity are decreased numbers of peripheral naïve T cells and the concomitant accumulation of late-stage differentiated memory T cells [18, 21–28] with reduced antigen receptor repertoire diversity [26, 29–31] (Figs. 14.1 and 14.2). This phenomenon results

from poorly understood age-related impairments in the hematopoietic stem cell (HSC) compartment which generates fewer T-cell precursors in adult and later life, on the one hand, and thymic involution at puberty which markedly reduces the production of mature T cells from their precursors, on the other hand [32].

The HSC compartment (Fig. 14.1) is negatively modulated and functionally affected by aging [33] and is increasingly substituted by adipose tissue [18, 34, 35]. Age-related modification within the HSC compartment may be partly due to the “intrinsic cellular aging” of HSCs themselves. Aged HSCs demonstrate more accumulated DNA damage, telomere attrition, and epigenetic deregulation, often in combination with an increase in intracellular reactive oxygen species (ROS) [2, 36]. Such events may also lead to progressive myeloproliferative disorders and the malignant transformation of HSCs. In addition to such “intrinsic” HSC age effects, the extracellular and stromal matrix of the aging bone marrow (which normally nurtures and drives stem cell production) also undergoes dramatic structural changes in terms of the numbers of stromal cells and osteoblasts and reduced production of IL-7 (Fig. 14.1). The aged pool of HSCs is often characterized by a marked shift in lymphoid and myeloid lineage output. Such age-associated myeloid skewing of the differentiation potential, together with decreased homing efficiency, contributes to changes in the cellular composition of the HSC compartment and is believed to be an important contributor to the decline of immune competence in the elderly [2, 37, 38].

Given the age-associated alterations at the level of immune cell production in the bone marrow and the skewing toward myeloid differentiation in the cells exported to the periphery, it is not surprising that immune functioning also changes with age. Not only are fewer B cells produced and fewer T-cell progenitors, but in the case of the latter, their development in the thymus is compromised by the universal process of thymic involution (Fig. 14.1). Although this may be viewed as a developmental event and not truly a senescence effect, it is thought to have dramatic consequences for immunity over the lifespan [18].



Both extrinsic and intrinsic factors are considered (Fig. 14.1) to be involved in causing thymic involution, including the thymic microenvironment as well as the impaired development of aged thymocytes themselves [39]. During this ongoing process, beginning even before puberty, as in the bone marrow, a progressive replacement of lymphoid tissue by fatty tissue takes place, accompanied by a reduction of the active areas of thymopoiesis [40]. Most elderly people do retain some residual thymic function, which may act to provide a continuous low-level input of new naïve T cells (Fig. 14.1) to the periphery [41] at least until extreme old age [18]. The end result of thymic involution is that the individual is equipped with a set of naïve T cells early in life, but which are not constantly replaced at the same level throughout life. Thus, elderly people have vanishingly small numbers of naïve T cells and accumulations of memory T cells (Figs. 14.1 and 14.2), mostly specific for the pathogens that they have previously encountered [18].

Aged individuals have decreased protection against newly arising infections as well as difficulties in controlling endogenous persistent viral infections [42]. According to a current paradigm, the age-associated shrinkage of compartment size and diminution in T- and B-cell receptor

diversity (Fig. 14.1) appears to be responsible for the impaired protective ability of the immune system to respond to a universe of antigens [25, 26, 42]. Particularly, dramatic changes with age are seen in the repertoire diversity that declines dramatically [29, 31].

Lifelong exposure to different pathogens (Figs. 14.1 and 14.2) is regarded as a major driving factor of the phenotypic changes in the distribution of T-cell subsets over the life course. For unclear reasons, especially a latent infection with cytomegalovirus (CMV), but not with any other herpes viruses, with recurrent episodes of reactivation has been found to promote memory T-cell “inflation” and drive T cells to a late stage of differentiation. In aged individuals, oligoclonally expanded CD8⁺ T cells show an increased expression of late-stage differentiation markers. The accumulation of these highly differentiated T cells, at least some of which may be truly senescent, contributes to the age-associated increased production of pro-inflammatory cytokines and low-grade inflammation and could thus possibly also contribute to age-related morbidity and mortality [24, 43–47].

Regulatory T cells (Tregs) play a central role in immune regulation (Fig. 14.1), providing a delicate balance between protective and patho-

Fig. 14.1 The aging immune system. The HSC compartment is negatively modulated and functionally affected by aging (a). Age-related modification within the HSC compartment may be partly due to “intrinsic cellular aging” of HSCs themselves, with accumulated DNA damage, telomere attrition, and epigenetic deregulation. The extracellular and stromal matrix also undergoes dramatic structural changes in terms of the numbers of stromal cells and osteoblasts and the reduced production of IL-7. The aged pool of HSC shows a marked shift in lymphoid and myeloid lineage output. Thymic involution (b) involves both extrinsic and intrinsic factors, including the thymic microenvironment as well as the impaired development of aged thymocytes themselves. A progressive replacement of lymphoid tissue by fatty tissue takes place, accompanied by a reduction of the active areas of thymopoiesis. The end result of thymic involution is vanishingly small numbers of naïve TC and accumulations of memory TC (c), mostly specific for the pathogens that they have previously encountered. Age-affected Tregs (d) can induce chronic inflammation, an increased risk of autoimmunity, but also be responsible for diminished immunity. Elevated inflammatory immune mediators, SARS (e), are responsible for the activation of self-reactive memory BC, producing increased levels of auto-Ab (f), which are frequent in aged individuals as a result of tissue damage and apoptosis. Repetitive antigenic challenges over the lifetime (g) may stimulate pro-inflammatory cytokines, contributing to the maintenance of persistent chronic inflammation. Self-reactive B and T cells (h) recognize a self-antigen and differentiate into memory and effector cells due to a breakdown of the control of autoreactivity. Chronic inflammation additionally resulting in tissue injury and apoptosis attracts DCs, which in elderly people have impaired the ability to take up apoptotic cells (i). Instead, they induce a vicious circle with a further pro-inflammatory response and increased reactivity to self-DNA, which may be more immunogenic in the elderly. Additionally, DAMPs (I), present in proteins released during cell necrosis, promote sterile inflammation. ECM, extracellular matrix; HSC, hematopoietic stem cell; TEC, thymic epithelial cells; ADPC, adipocytes; OB, osteoblasts; DC, dendritic cells; FB, fibroblasts; BM, bone marrow; BC, B cells; TC, T cells; auto-TC, autoreactive T cells; Tregs, regulatory T cells; MDSCs, myeloid-derived suppressor cells; ApoptB, apoptotic bodies; DNA, deoxyribonucleic acid; DAMPs, damage-associated molecular patterns; SASP, senescence-associated secretory phenotype; IL, interleukin; Auto-Ab, autoantibodies. (Modified from Müller and Pawelec [18])

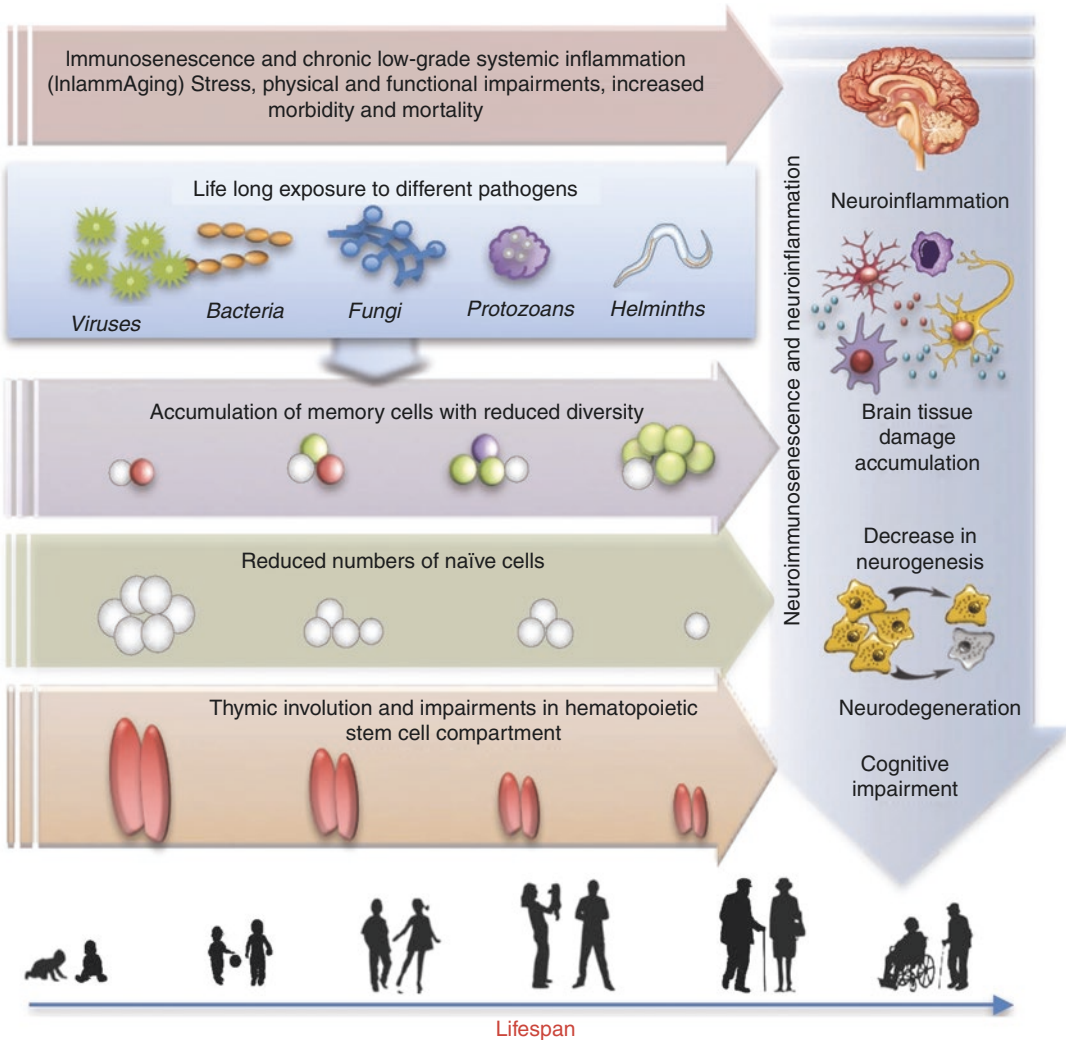


Fig. 14.2 Potential mechanisms of immunosenescence and neurosenescence. Immunosenescence affects both adaptive and innate immune systems. The most relevant changes to adaptive immunity are decreased peripheral naïve T cells and the concomitant accumulation of late-stage differentiated memory T cells with reduced antigen receptor repertoire diversity. This phenomenon results from age-related impairments in the hematopoietic stem cell compartment and thymic involution. Lifelong exposure to different pathogens is the major

driver of the phenotypic changes in the distribution of T-cell subsets over the life course. Aging is characterized by a chronic, low-grade inflammation (inflammaging). Peripheral immunosenescence and inflammaging may promote neuroinflammation by modulating glial cells toward a more active pro-inflammatory state, leading to a loss of neuroprotective function, to neuronal dysfunction accumulation of brain tissue damage, and to neurodegeneration. (Modified from Di Benedetto et al. [65]. <https://doi.org/10.1016/j.neubiorev.2017.01.044>)

genic immune responses [18]. Early data indicated that younger and older people possessed phenotypically identical Tregs but that suppressive function waned in the latter [48]. More recent data confirm that aging significantly

affects the generation, homeostasis, diversity, and functional competence of Tregs. A decline of thymic function disturbs the thymic Treg production and also seems to be compensated for through the peripheral expansion of

pre-existing Tregs and/or through the conversion of conventional T cells into Tregs [49], as had been demonstrated using T-cell clonal culture models much earlier [50]. Thus, due to the leading role of Tregs in immune homeostasis, an age-related deterioration of Tregs (Fig. 14.1) might induce either excessive immunity (impacting a chronic inflammation as well as increasing the risk for autoimmunity) or, conversely, an age-related increase of Treg activity might result in failing immunity (raising the risk of malignancies and infectious diseases) in the elderly [49, 51, 52].

As we age, the maintenance of homeostatic conditions may become compromised [18]. The consequence of this imbalance may be that immunity is redirected toward the innate immune responses, characterized by increased levels of systemic inflammatory molecules – a phenomenon dubbed as inflammaging [44]. Large epidemiologic studies commonly report about elevated levels of inflammatory factors such as CRP, IL-6, and TNF in the peripheral blood of elderly people [53].

Elevated inflammatory immune mediators (Fig. 14.1) are thought to be involved in most age-related chronic and neurodegenerative diseases as well as carcinogenesis. Over the life course, inflammatory stimuli from pathogen sources are likely to become increasingly entangled with endogenous stimuli. One possible source of this endogenous “noise” is the senescence-associated secretory phenotype (SASP) characterizing the accumulating “senescent” cells in the elderly that can affect the behavior of neighboring cells [54, 55]. The SASP is a spectrum of pro-inflammatory proteins and cytokines secreted by such cells, which have permanently exited the cell cycle and are known to accumulate in the periphery to significant numbers with advancing age [56, 57].

This process is also associated with the activation of self-reactive memory B cells, producing increased levels of autoantibodies (Fig. 14.1), which are frequent in aged individuals as a result of tissue damage and apoptosis [58]. Repetitive antigenic challenges over a lifetime (Figs. 14.1

and 14.2) may stimulate pro-inflammatory cytokines, contributing to the maintenance of persistent chronic inflammation [59]. Such persistent age-related chronic inflammation represents an extreme stress factor for the immune system, causing eventual exhaustion. Autoimmunity is associated with what could be considered premature immune aging, demonstrating the relationship between chronic immune stimulation and progressive immunosenescence [18, 60].

According to the current paradigm, autoimmunity develops when self-reactive B and T cells (Fig. 14.1) recognize a self-antigen and differentiate into memory and effector cells due to the breakdown of the control of autoreactivity [15]. It can occur by a selection of T cells with an elevated affinity for self-antigens or latent viruses, which are at the same time also pro-inflammatory. The chronic inflammation additionally resulting in tissue injury and apoptosis attracts dendritic cells (DC), which in elderly people have an impaired ability to take up apoptotic cells (Fig. 14.1). Instead, they induce a vicious circle with a further pro-inflammatory response and increased reactivity to self-DNA, which may be more immunogenic in the elderly due to increased hypomethylation [16]. Additionally, damage-associated molecular patterns (DAMPs), present on proteins released during cell necrosis and promoting sterile inflammation, also become more frequent with advancing age [17, 18].

It has been suggested that aging is associated with chronic innate immune activation and significant changes in the functions of monocytes and macrophages, which may have implications for increased low-grade chronic inflammation and for the development of age-related diseases [61]. Monocytes are known to be mediators of the inflammatory response and comprise at least three different subsets, namely, classical, intermediate, and nonclassical monocytes. An age-related increase in frequencies of intermediate and nonclassical monocytes has been reported [62, 61]. Our results from the Berlin Aging Study II confirmed these findings, where we also found an age-related increase in frequencies of intermediate and nonclassical monocytes [63]. Together with

age-related macrophage activation, inflammatory monocytes contribute to the subclinical chronic inflammatory process [44, 64, 65].

The immune and central nervous systems represent two adaptive physiological systems of the body, which extensively communicate with each other throughout the lifespan. Given the multifaceted interactions between these systems and their tight interdependency, it is to be expected that peripheral immunosenescence and inflammaging contribute to neuroinflammation. Peripheral low-grade inflammation may promote inflammatory processes in the aged brain (Fig. 14.2) by modulating glial cells toward a more active pro-inflammatory state, leading to the loss of neuroprotective function, to neuronal dysfunction, and to the accumulation of brain tissue damage [65–67]. Systemic inflammation may, therefore, increase the risk of developing cognitive impairment, neurological disorders, and neurodegeneration [68–70]. In the next section, we will have a closer look at how inflammaging may contribute to the process of neuroinflammation during aging.

Neuroinflammation and the Aging Brain

Human aging is characterized by an impairment of cognitive abilities. Although no agreement exists on the basic mechanisms involved in this process, neuroinflammation appears to be the main contributor that links together many factors associated with cognitive aging [65, 71]. As we age, we experience greater susceptibility to memory impairments following an immune challenge that is characterized by an increased and prolonged production of pro-inflammatory cytokines in the otherwise healthy aged brain [65, 72]. It is widely established that both aging and stress can affect the neuroendocrine system, activate the hypothalamic-pituitary-adrenal (HPA) axis to release corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus, and cause the anterior pituitary gland to secrete adrenocorticotropin (ACTH) (Fig. 14.3). This, in turn, induces the release of glucocorti-

coids from the adrenal gland into the circulation [73]. Cortisol affects the immune system in different ways by regulating the expression of cytokines [74], chemokines, and adhesion molecules and by affecting immune cell migration, maturation, and differentiation [65, 72, 75]. High levels of cortisol can negatively influence hippocampal neurogenesis directly or indirectly through the regulation of the expression of cytokines and their receptors on the brain and immune cells.

Recent ultrastructural analyses have uncovered a new player in the age-related remodeling of neuronal circuits, especially at the synapse level, that is rare under homeostatic conditions but becomes abundant during aging, neurodegeneration, and chronic stress [76]. These hyperactive “dark microglia” (Fig. 14.3) frequently reach into synaptic clefts with their highly ramified and thin processes, extensively encircle axon terminals and dendritic spines, and engulf them [76, 77]. Aging and neurodegeneration are characterized by dysregulated interactions with synapses, resulting in neuronal loss, which, in turn, represents the best pathological correlate of cognitive decline [77]. These conditions can sensitize the aged brain to produce an exaggerated response following exposure to a stressor or to the presence of an immune stimulus in the periphery [78]. Altered microglia profiles together with impairments in key regulatory systems can lead to prolonged neuroinflammation and age-related neurobehavioral complications [65, 79].

On the systemic level, peripheral immunosenescence and inflammaging lead to age-related changes in the blood (Fig. 14.3) [65]. Chronic exposure to inflammatory mediators may disrupt the endothelial barrier and allow for the transfer of immune cells and numerous pro-inflammatory cytokines into the brain parenchyma that, in turn, can modulate microglial phenotype and reactivity and drive low-grade brain inflammation. Brain cells, such as microglia, astrocytes, and neurons, as well as peripheral immune cells, such as T cells, monocytes, and macrophages, participate in inflammation (Fig. 14.3). It would provide an inflammatory milieu that is populated by all these resident and additional infiltrating immune cells that participate in a complex inter-

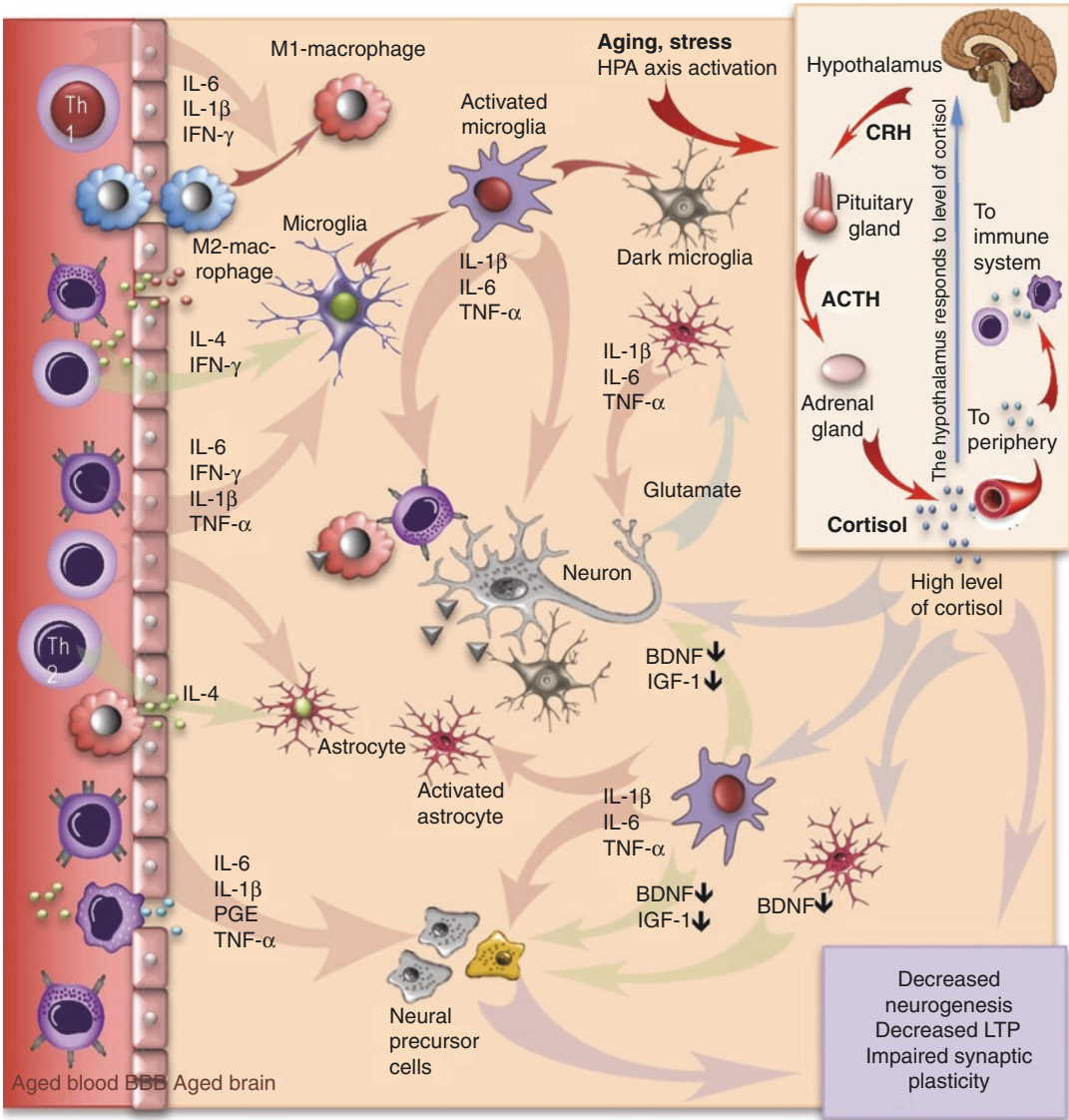


Fig. 14.3 The aging brain and neuroinflammation. Aging and stress activate the HPA axis to release CRH from the paraventricular nucleus of the hypothalamus and cause the anterior pituitary gland to secrete ACTH. This, in turn, induces the release of glucocorticoids from the adrenal gland into the circulation. High levels of cortisol can negatively influence hippocampal neurogenesis directly or indirectly through the regulation of an expression of cytokines and their receptors on the brain and immune cells. Peripheral immunosenescence and inflammaging lead to age-related changes in the blood. Chronic exposure to inflammatory mediators may disrupt the endothelial barrier and allow for the transfer of immune cells and numerous pro-inflammatory cytokines into the brain parenchyma that, in turn, can modulate microglial phenotype and reactivity and drive low-grade brain inflammation. Activated microglia and astrocytes change

their morphology and function and produce pro-inflammatory cytokines, such as IL-1 β , IL-6, and TNF. Macrophages change their protective M2-phenotype to the pro-inflammatory M1-phenotype, thus contributing to further neuroinflammation. This overproduction of pro-inflammatory mediators disrupts the delicate balance needed for LTP induction, impairs synaptic plasticity, and reduces the production of BDNF and IGF-1, thus having detrimental consequences for neural precursor cells as well as for the normal neuronal functioning. HPA, hypothalamic-pituitary-adrenal axis; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; LTP, long-term memory potentiation; BDNF, brain-derived neurotrophic factor; IGF, insulin-like growth factor. (Modified from Di Benedetto et al. [65]. <https://doi.org/10.1016/j.neubiorev.2017.01.044>)

play between secreted inflammatory modulators and activated cell surface receptors, such as Toll-like receptors (TLRs) [65]. These receptors are primarily expressed on cells that play central roles in inflammatory response, including macrophages and microglia [80].

Activated microglia and astrocytes change their morphology and function and produce pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF [65]. Recent work suggests that microglia undergo a process of senescence, similar to the one in peripheral immune cells. Senescent and hyperactive microglia have been detected in the aged and diseased brain [81]. The aging brain, in turn, is apparently able to modulate the immune system and to support the recruitment of immune cells from the periphery, thereby contributing further to immunosenescence and neuroinflammation [82]. In addition, macrophages change their protective M2-phenotype to the pro-inflammatory M1-phenotype, thus contributing to further neuroinflammation [65]. As the aged brain is already “primed” to respond to inflammatory stimuli, additional stress or infection may induce more detrimental changes in the cognitive functioning of aged individuals [78, 83]. Furthermore, the age-related concurrent reduction of anti-inflammatory molecules also contributes to a sensitization to extrinsic and intrinsic stressors. T cells produce less IL-4 and IL-10 and more interferon gamma (IFN- γ), thereby promoting microglial activation. This has detrimental consequences for neural precursor cells, leading to a decrease of neurogenesis (Fig. 14.3) as well as increased decrements in learning and memory [84, 85].

Taken together, the overproduction of pro-inflammatory mediators in the periphery may induce a progressive increase in neuroinflammation, characterized by increased glial activation, elevated steady-state levels of inflammatory cytokines, and a decreased production of anti-inflammatory molecules, even in neurologically intact aged individuals [65]. In the next section, we consider the modulatory potential of nutrition in its ability, in combination with physical activity, to mediate anti-inflammatory effects and thus positively influence immunity and the aging brain.

The Impact of Nutrition and Physical Activity

Evidence that long-term behavioral changes, including nutritional intervention and reduced energy intake together with physical activity, may prevent, improve, or even reverse age-related impairments in immune function continues to accumulate [2]. Lifestyle factors, such as diet and exercise, have been established as playing an important role in immunosenescence, and the practice of “healthy” behavior may minimize the age-associated decline of immune function (Figs. 14.4 and 14.5).

Accumulating data strongly suggest that inflammation and oxidative stress are the main inducers of cellular aging (Fig. 14.5). The cross talk between oxidative stress and inflammation is a complex process, and there are studies reporting that ROS can stimulate inflammation via the activation of inflammasomes and the production of cytokines such as IL-1 β and IL-18, which subsequently trigger inflammatory responses [86].

At least in the context of adiposity and inflammation mentioned above, as well as via multiple other postulated physiological effects, caloric restriction (CR) in humans might have beneficial effects in terms of lowering metabolism, a reduction of visceral fat, and weight loss [2]. CR has been shown to delay signs of immunosenescence in animals and is considered today as the only known method to prolong median as well as maximal lifespan in several tested species, from invertebrates to rodents and even including non-human primates [32, 87]. Thus, in rodents and nonhuman primates, CR leads to an attenuation of the age-related shift from naïve to memory-phenotype T cells and maintains a higher number of naïve T cells in aged animals [88]. Furthermore, the age-associated rise of pro-inflammatory cytokines, such as IL-6, IFN- γ , and TNF, and the resulting pro-inflammatory state of an aged immune system can be reversed by CR. It has been reported that the age-related decrease in the proliferative capacity of T cells (due to the shift from naïve to memory-phenotype T cells) can be reversed by CR [2, 32].

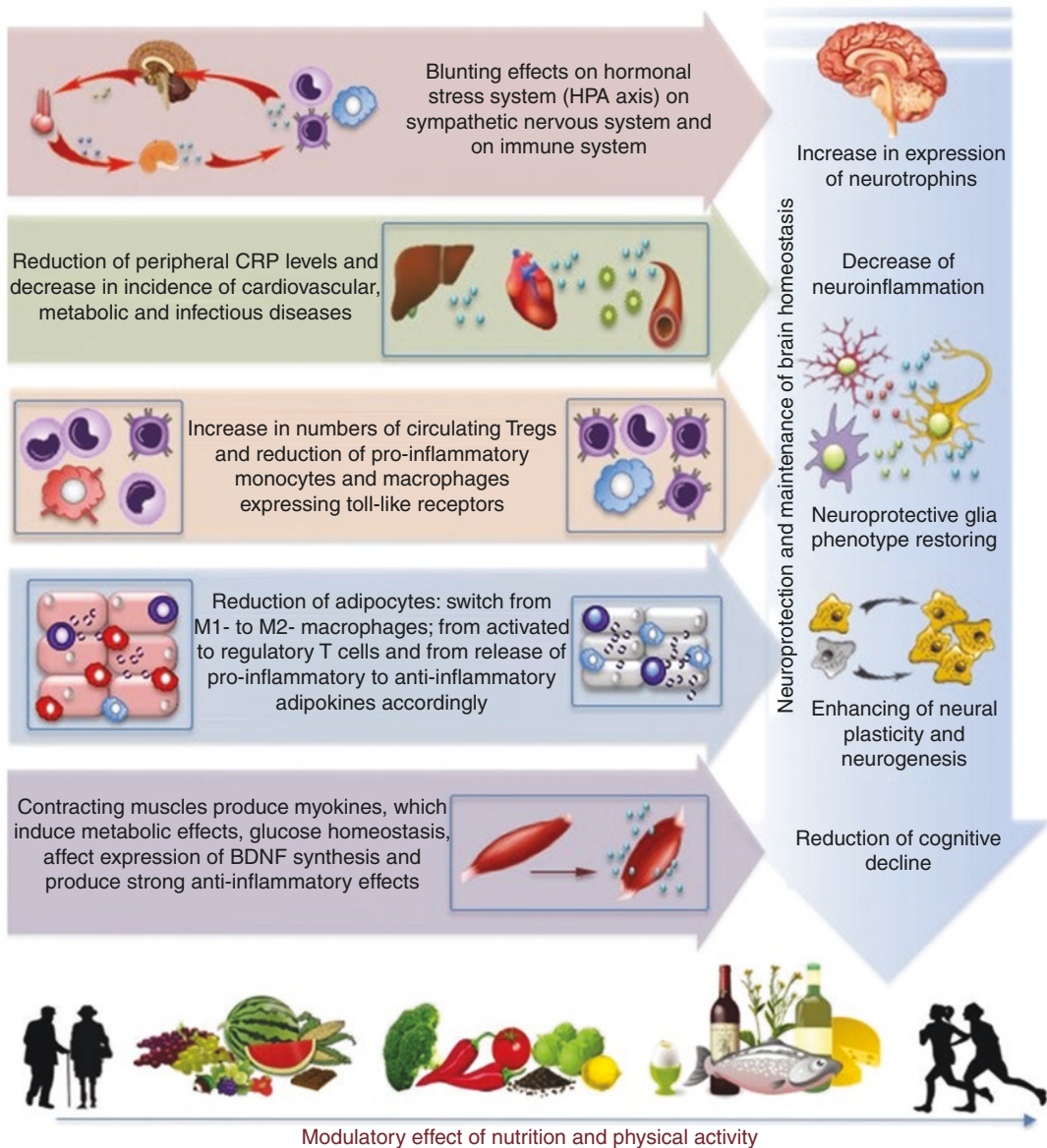


Fig. 14.4 Potential effects of nutrition and physical activity on immunoneurosenescence. HPA, hypothalamic-pituitary-adrenal axis. (Modified from Di Benedetto et al. [65]. <https://doi.org/10.1016/j.neubiorev.2017.01.044>)

Nevertheless, there are still many open questions concerning CR, which has been shown to be effective in improving the immune response in unchallenged animals, although it might compromise the host's defense against pathogenic infection and result in higher morbidity and mortality outside the laboratory. Moreover, CR has been shown to delay immunosenescence in animals,

but this effect needs to be verified in humans. Furthermore, short-term CR may well be feasible, whereas long-term dietary restriction might have detrimental psychological and other effects in humans, especially in the older population, making its practicality questionable [2, 89, 90]. Nevertheless, the recent results from a multi-centered, randomized clinical trial have

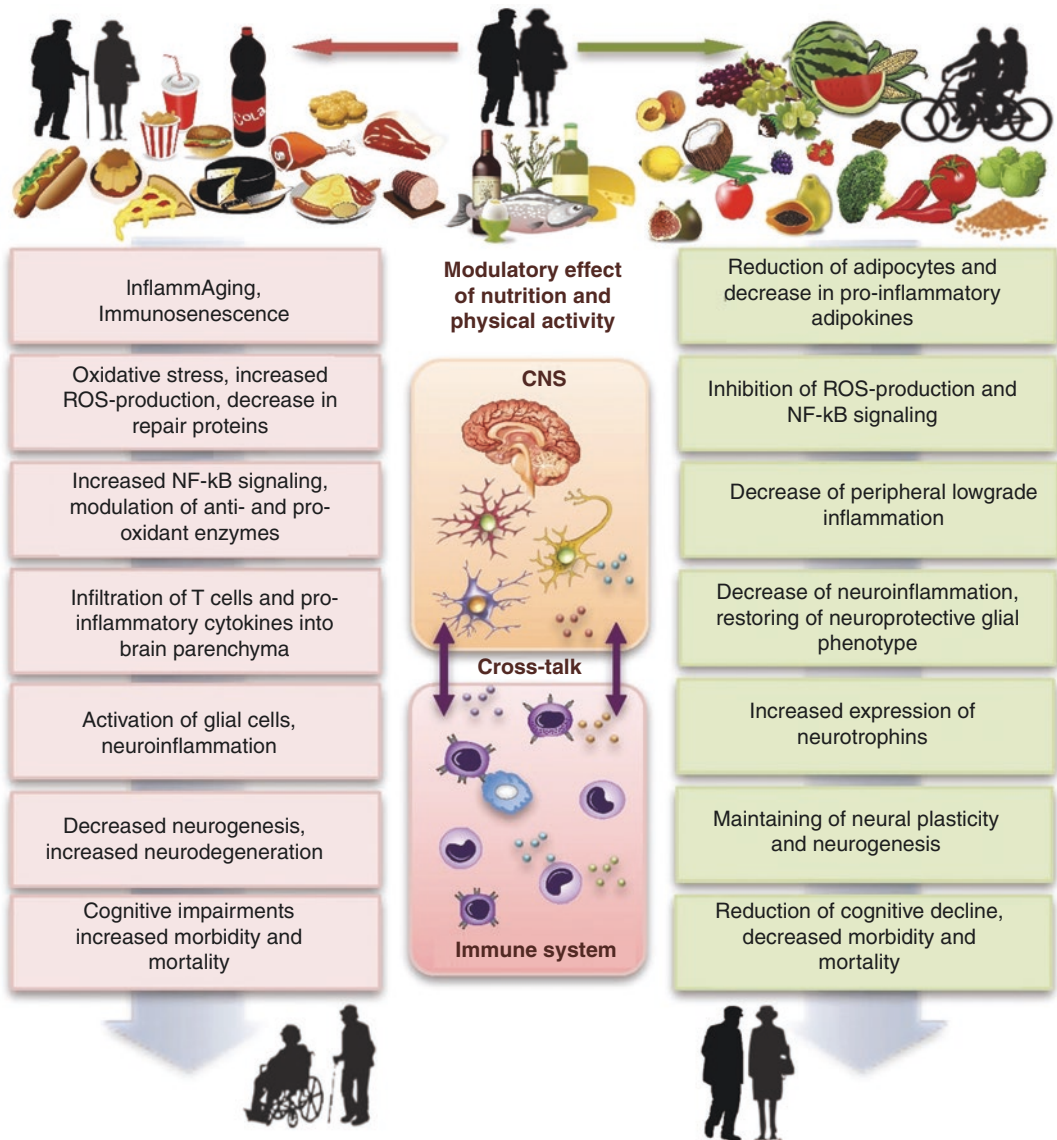


Fig. 14.5 An overview of the age-related effects and the modulatory potential of nutrition and physical activity on immunoneurosenescence. (Modified from Di Benedetto et al. [65]. <https://doi.org/10.1016/j.neubiorev.2017.01.044>)

demonstrated that long-term moderate CR without malnutrition induces a significant and persistent inhibition of inflammation in young and middle-aged healthy nonobese adults without impairing the cell-mediated immunity [91].

The optimization of nutrition may represent one of the first and theoretically easiest and cheapest strategies that can be employed to preserve health during aging [2]. The development of “elderly specific,” functional foods, containing

probiotics and/or prebiotics, may help in preventing the age-related disruption of the gut environment [92]. In fact, it has been demonstrated that the maintenance of a “healthy” gut microbiota during aging could help to delay or prevent the inflammaging process [93].

Immunostimulatory properties, such as the modulation of cytokine production or adjuvant effects on T-lymphocytes and NK activity, have been demonstrated for various health-promot-

ing *Lactobacillus* and *Bifidobacterium* strains [94–96]. It has been shown that 3- and 6-week interventions in elderly people can have positive effects, such as measurable increases of NK cells, tumoricidal activity, and monocyte phagocytic capacity [97]. A probiotic yogurt supplementation tested on elderly persons affected intestinal bacterial overgrowth. This intervention was able to normalize the response to endotoxin and modulate inflammatory markers in blood [98] as well as decrease the incidence of infections in this group of elderly people. Furthermore, a significant increase of phagocytosis, NK-cell activity, and production of IL-10 was also demonstrated following the probiotic supplementation in the elderly as well as the reduced production of the pro-inflammatory cytokines IL-6, IL-1 β , and TNF [92, 99]. Boge et al. showed in two clinical trials that the consumption of a probiotic drink (containing *L. casei*) by elderly subjects for several weeks before and after an influenza vaccination led to a significant increase in the influenza-specific antibody titer, demonstrating the potential of probiotics in improving the protective efficacy of vaccination in the elderly population, in which it is usually considerably reduced [100, 101].

A seminal advance has been the realization that probiotic supplementation is likely to require “tailor-made” mixtures of different bacteria in order to achieve the desired effect. Atarashi et al. identified 17 strains of bacteria preferentially inducing colonic Tregs which reduced symptoms in models of colitis and allergic diarrhea in mice [102]. Thus, supplementation with tailor-made mixtures of probiotics may be effective in modulating immune responses where the use of single strains is ineffective. This may be one reason why the results of the many human probiotics supplementation trials have often been equivocal since mostly a single strain was used even if it was the “right” strain [2]. The mechanism of action of the mixed bacterial strains is the induction of CD4⁺ CD25⁺ FOXP3⁺ Tregs by bacterial antigens, which in turn stimulate the intestinal epithelial cells to produce TGF- β 1, but not inflammatory IL-6, and TNF. Fecal samples from patients with

inflammatory bowel disease and atopy have been reported to contain relatively low amounts of some of the same bacterial strains, suggesting their relevance to human disease as well as in the animal model.

In the context of supporting the “right” balance of gut bacteria, reversing our nutritional habits “back to mother nature” might represent an additional solution for the modulation of age-related inflammatory status and associated chronic and neurodegenerative diseases [2]. The accumulating data from in vitro, animal, and clinical studies provide evidence that a greater consumption of fruits, cereals, vegetables, legumes, and spices is associated with a lower risk of many diseases [103–108]. Consumption of diets consisting of natural foods can also raise the amounts of plant-based nutraceuticals in the body, such as antioxidants and anti-inflammatory agents. These nutraceuticals are known to cope with free radicals and to modulate the inflammatory signaling pathways in cells, suppressing the onset of age-related chronic conditions [2, 107, 109–111].

Several studies demonstrate that dietary polyphenols are able to repress inflammation by the inhibition of nuclear factor kappa-light-chain enhancer of activated B-cell (NF- κ B) signaling [112–116]. Remarkably, plant extracts from strawberry, mulberry, and blueberry were shown to contain antioxidants that are able to activate the antioxidant defense system and to counter the deleterious effects of irradiation by reducing oxidative stress and inflammation [117]. A significant decrease in the levels of inflammatory cytokines was demonstrated by the administration of the diet supplements containing pomegranates, figs, or dates [118].

Nutritional intervention including micronutrients and vitamins has also been recognized as a practical, cost-effective approach to attenuate age-associated declines in immune function, vaccination efficiency, and resistance to infectious and neoplastic diseases. The importance of micronutrients, trace elements, and vitamins in proper immune functioning is clear, and deficiencies in one or more of these nutrients may impair practically all forms of immunity [2]. Among

them, zinc is an essential element of which the significance to health is indisputable, as discussed above [119]. It has been shown that zinc supplementation enhances the innate immune responses by increasing phagocytosis and T-cell functionality [120]. An increase in serum zinc concentration was associated with an increase in the number of T cells [119]. Zinc supplementation was also able to improve the generation of NK cells from CD34⁺ cell progenitors through the increased expression of the GATA-3 transcription factor [7].

Vitamin C has also been found to positively modulate immunosenescence and inflammaging, representing two main hallmarks of human aging. Moreover, it has been shown to epigenetically regulate genome integrity and stability, indicating a key role of vitamin C in healthy aging [121].

Vitamin E supplementation has been demonstrated to improve immune responsiveness in healthy elderly individuals by the enhancement of cell-mediated immunity [122]. It was also able to reverse many of the T-cell age-associated defects, including reduced levels of phosphorylation of critical signaling proteins, as well as to improve defective immune synapse formation. Vitamin E also enhances the production of IL-2, the expression of several cell cycle control proteins, and T-cell proliferation [123]. Intake of vitamin E above recommended levels has been shown to enhance T-cell function in aged animals and humans. This effect is believed to contribute to an improved resistance to influenza infection and to a reduced incidence of upper respiratory infections in elderly people [1, 124].

Here, we can provide only a few examples, limited to spices and fruits and their bioactive components, known to modulate different stages of tumorigenesis, including tumor cell survival, proliferation, invasion, and angiogenesis. The anticancer activities of spices are mediated primarily through the suppression of inflammation. Bioactive components of spices, such as eugenol and 6-gingerol, prevent the release of TNF and IL-1 β [125] in vitro stimulated macrophages [126]. Curcumin has been shown to suppress the inflammatory mediators NF- κ B and COX-2 [127], anethole inhibits NF- κ B activation and

cytokine production [128], and cinnamaldehyde blocks the age-related activation of NF- κ B and targets inflammatory COX-2 as well as induces nitric oxide synthase (NOS) [129]. Ursolic acid, which is present in many fruits, including apples, pears, plums, bearberries, loquat, jamun, and rosemary, has been found to exert antitumor activity against colon cancer [130], breast cancer [131], nonsmall cell lung cancer [132], pancreatic cancer [105], melanoma [133], multiple myeloma [134], cervical cancer [135], and prostate cancer [108]. Also, several other nutraceuticals have been shown to exert antitumor and anti-inflammatory activities.

Since oxidative stress and inflammation are two of the major triggers of age-related pathologies and neurodegeneration, the consumption of phytochemicals from fruits, vegetables, herbs, and spices may exert relevant immunomodulatory and anti-inflammatory activities also in the context of the aging brain [86]. Compelling evidence has shown that dietary phytochemicals, particularly polyphenols, have properties that may suppress neuroinflammation and prevent toxic and degenerative effects in the brain. The mechanisms by which polyphenols exert their action are not fully understood, but it is clear that they have a direct effect through their antioxidant activities. They have also been shown to modulate intracellular signaling cascades, including the PI3K-Akt, MAPK, Nrf2, and MEK pathways. Polyphenols also interact with a range of neurotransmitters, illustrating that these compounds can promote their health benefits in the brain through a direct, indirect, or complex action [136]. Approaches with multiple antioxidant nutrients to block the oxidative stress related to the systemic and brain inflammation pathways may, therefore, prevent or delay the cognitive impairments by preventing microglia aging [137].

As a framework of balanced multicomponent diet strategy, adherence to a Mediterranean diet enriched with fruits, vegetables, nuts, and unsaturated fatty acids promotes neuroprotection by decreasing inflammation, restoring cerebral blood flow and volume, inhibiting neurodegeneration, and enhancing neural plasticity by increasing neurogenesis [138].

Flavonoids, plant polyphenolic compounds, which are abundant in fruits and vegetables, exhibit a wide variety of biological effects, including antioxidant, free-radical scavenging, and anti-inflammatory properties. Luteolin, a flavonoid found in high concentrations in celery and green pepper, has been shown to reduce the production of pro-inflammatory mediators and to inhibit the JNK and AP-1 signaling pathway in mice [139]. It was therefore suggested that luteolin may inhibit neuroinflammation and improve cognition in the otherwise healthy aged by constraining brain microglia [140].

Phenolic acids, an important class of polyphenols, are abundantly present in berries, nuts, coffee, tea, and whole grains. They exert their antioxidant and anti-inflammatory activities by the attenuation of microglial activation; the significant inhibition of the production of TNF, IL-6, IL-1 β , and NO; and the reduction of mRNA and protein levels of COX-2 and iNOS [141]. Also, retinoids and carotenoids are known as potent antioxidants and anti-inflammatory agents having neuroprotective properties [142]. Sesamol, a phenolic lignan from sesame supplementation, prevents systemic inflammation-induced memory impairment [143].

Recently, much interest has focused on the suggested anti-inflammatory and neuroprotective effects of dietary-derived polyphenols and the long-chain n-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), rendering these molecules as potential candidates for use in preventative and therapeutic strategies to reduce the risk of age-related chronic neurodegenerative diseases [144–146]. Both DHA and EPA can reduce neuroinflammation and cognitive decline. In particular, it has been demonstrated that EPA positively influences mood disorders and DHA maintains normal brain structure [147]. Supplementation with EPA may attenuate neuroinflammation by inhibiting microglial activation and microglia-produced pro-inflammatory cytokines and by enhancing the expression of astrocyte-produced neurotrophins and their receptors [148].

In general, many studies with animal models support the protective effects of n-3 PUFA

supplementation under different conditions. However, studies to demonstrate clear benefits on human subjects toward a particular disease have not been conclusive, probably due to heterogeneous dietary habits and the population being in different demographic conditions. Since many botanical polyphenols can also up- and downregulate the same pathways, future studies may need to include testing for combined effects of DHA and these polyphenols [149]. Thus, more clinical studies are needed to determine the amounts of dietary agents needed to delay aging and age-related diseases and to investigate their effects on different age groups [107]. Furthermore, when identifying dietary approaches to promote healthy brain aging, a holistic approach should be considered, including nutrition, exercise, and lifestyle factors, which not only target the brain but also overall cardiovascular, immune, and metabolic health [144].

Several interventions, including different types of exercises, have been proposed to restore immune and neural functions in elderly people. Physical exercise and physical activity in later life might target modifiable risk factors of aging, such as low-grade inflammation, inducing immunoprotective and neuroprotective functions (Fig. 14.5) [150, 151]. Numerous studies have revealed the anti-inflammatory and antioxidative effects following physical activity (Figs. 14.4 and 14.5), which potentially exert beneficial effects on neuroplasticity, affect the expression of neurotrophins, and therefore help to maintain normal neuronal functions [152]. Barrientos and colleagues observed an inhibition of neuroinflammation (caused by infection) in rats performing exercises and an increased induction of BDNF mRNA in the brain of otherwise sedentary animals [153]. Further studies with aged mice revealed that wheel running inhibits the pro-inflammatory state of microglia and their ability to proliferate, thus inducing a pro-neurogenic phenotype [154].

Certainly, the anti-inflammatory effects of exercise are mediated through multidirectional pathways. Some of them are exerted on adipose tissue, skeletal muscles, immune system cells, and the cardiovascular system (Figs. 14.4

and 14.5). These effects include the modulation of anti-inflammatory and pro-inflammatory cytokine profiles, redox-sensitive transcription factors, and antioxidant and prooxidant enzymes and repair proteins [155]. Regular physical activity combined with nutritional interventions can reduce the size of adipocytes and attenuate inflammation in adipose tissue by phenotype switching from pro-inflammatory M1-type to anti-inflammatory M2-type macrophages (Fig. 14.4). In addition, a reduction in the numbers of circulating pro-inflammatory-type monocytes and an increase in the numbers of Tregs were found in the peripheral blood of individuals following physical activity [156, 157].

Recent evidence suggests that contracting muscles release myokines [2, 158–162], which affect the synthesis of BDNF in the dentate gyrus of the hippocampus [162]. Physical activity may have a buffering role on the hormonal stress-responsive systems (Fig. 14.4), such as the HPA axis and the sympathetic nervous system [163], thus maintaining immunoprotective and neuroprotective functions. It has been also shown that regular exercise is associated with an improved immune responsiveness to influenza vaccination in older adults. The exercise-related increase in the antibody titer, T-cell function, macrophage response, improvement of the Th1/Th2 cytokine balance, the level of pro-inflammatory cytokines, and changes in naive/memory cell ratio have also been reported [164].

Taken together, one might conclude that nutritional intervention in combination with physical activity activates and/or modulates the release of hormones, myokines, and cytokines as well as modulate the expression of various immune-reactive molecules, which all contribute to anti-inflammatory effects and the possible attenuation of immunosenescence and neuroinflammation.

Conclusions

Around the world, especially in many European countries, the older segment of the adult population is growing in size and proportion [165]. In

dealing with this demographic change, what people make of the added years of their lives will be the most important aspect but will only be advantageous to the individual and to society at large if people can remain active participants in daily life and work [65]. Maintaining immunological and cognitive functions will be paramount, but their performances are known to decrease with increasing age, even in overtly healthy individuals. Preventing and/or attenuating immunosenescence and inflammation and delaying cognitive decline are probably the most effective measures for postponing the point of time at which individuals are no longer able to lead an independent life [65]. Effective pharmacological treatments, especially for cognitive but also for the immune decline, remain unavailable. Therefore, we will need a more holistic view of the aging process, where the dynamics of the interaction between environment, intestinal microbiota, and host must be taken into consideration. We should also take into account the age-associated physiological changes in the gastrointestinal tract as well as age-related modifications in lifestyle, nutritional behavior, and impaired functionality in the immune system of the elderly population [2, 65]. Some modifiable lifestyle factors, such as poor diet and physical and cognitive inactivity, have been identified as being associated with an increased risk of cognitive and immune decline [166]. Encouragingly, exercise can have a protective effect, even if initiated in advanced old age [2, 65, 167]. The intake of antioxidant nutrients reduces both systemic inflammation and neuroinflammation during aging [168]. Due to the fact that diet component targets are different, combining different nutrients acting on convergent anti-inflammatory pathways may result in an increased anti-inflammatory efficacy [144, 169, 170].

In this chapter, we have described the potential basic processes underlying age-related decline, namely, immunosenescence and a progressive increase in neuroinflammation characterized by an increased glial activation, elevated steady-state levels of inflammatory cytokines, and a decreased production of neurotrophic molecules as well as potential positive effects of nutrition and physical exercise. It is our

hypothesis, as partly summarized here, that a judicious combination of dietary interventions and exercise, cognitive training, and a pharmacological manipulation of immunosenescence and inflammatory processes will eventually deliver an optimal individualized regime for the maintenance of the best possible immune and cognitive functions over the lifespan of every individual.

Acknowledgment This research was supported by the Max Planck Society.

References

- Pae M, Meydani SN, Wu D. The role of nutrition in enhancing immunity in aging. *Aging Dis*. 2012;3(1):91–129.
- Müller L, Pawelec G. Aging and immunity – impact of behavioral intervention. *Brain Behav Immun*. 2014;39:8–22.
- Duncan SH, Flint HJ. Probiotics and prebiotics and health in ageing populations. *Maturitas*. 2013;75(1):44–50.
- Calder PC, Kew S. The immune system: a target for functional foods? *Br J Nutr*. 2002;88(Suppl 2):S165–77.
- Chasapis CT, Loutsidou AC, Spiliopoulou CA, Stefanidou ME. Zinc and human health: an update. *Arch Toxicol*. 2012;86(4):521–34.
- Mocchegiani E, Muzzioli M, Giacconi R, Cipriano C, Gasparini N, Franceschi C, et al. Metallothioneins/PARP-1/IL-6 interplay on natural killer cell activity in elderly: parallelism with nonagenarians and old infected humans. Effect of zinc supply. *Mech Ageing Dev*. 2003;124(4):459–68.
- Muzzioli M, Stecconi R, Moresi R, Provinciali M. Zinc improves the development of human CD34+ cell progenitors towards NK cells and increases the expression of GATA-3 transcription factor in young and old ages. *Biogerontology*. 2009;10(5):593–604.
- Sears B, Ricordi C. Anti-inflammatory nutrition as a pharmacological approach to treat obesity. *J Obes*. 2011;1–14.
- Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol*. 2011;11(2):85–97.
- Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*. 2011;11(9):607–15.
- White KA, Hutton SR, Weimer JM, Sheridan PA. Diet-induced obesity prolongs neuroinflammation and recruits CCR2(+) monocytes to the brain following herpes simplex virus (HSV)-1 latency in mice. *Brain Behav Immun*. 2016;57:68–78.
- Ornish D, Lin J, Daubenmier J, Weidner G, Epel E, Kemp C, et al. Increased telomerase activity and comprehensive lifestyle changes: a pilot study. *Lancet Oncol*. 2008;9(11):1048–57.
- Ford ES, Bergmann MM, Kroger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam study. *Arch Intern Med*. 2009;169(15):1355–62.
- Ornish D, Lin J, Chan JM, Epel E, Kemp C, Weidner G, et al. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *Lancet Oncol*. 2013;14(11):1112–20.
- Goronzy JJ, Li G, Yang Z, Weyand CM. The janus head of T cell aging – autoimmunity and immunodeficiency. *Front Immunol*. 2013;4:131.
- Gupta S, Agrawal A. Inflammation & autoimmunity in human ageing: dendritic cells take a center stage. *Indian J Med Res*. 2013;138(5):711–6.
- Pawelec G, Goldeck D, Derhovanessian E. Inflammation, ageing and chronic disease. *Curr Opin Immunol*. 2014;29:23–8.
- Müller L, Pawelec G. As we age: does slippage of quality control in the immune system lead to collateral damage? *Ageing Res Rev*. 2015;23(Pt A):116–23.
- Fulop T, Witkowski JM, Pawelec G, Alan C, Larbi A. On the immunological theory of aging. *Interdiscip Top Gerontol*. 2014;39:163–76.
- Walford RL. The immunologic theory of aging. Copenhagen: Munksgaard; 1969.
- Ben-Smith A, Gorak-Stolinska P, Floyd S, Weir RE, Lalor MK, Mvula H, et al. Differences between naive and memory T cell phenotype in Malawian and UK adolescents: a role for Cytomegalovirus? *BMC Infect Dis*. 2008;8:139.
- Di Benedetto S, Derhovanessian E, Steinhagen-Thiessen E, Goldeck D, Muller L, Pawelec G. Impact of age, sex and CMV-infection on peripheral T cell phenotypes: results from the Berlin BASE-II Study. *Biogerontology*. 2015;16(5):631–43.
- Malaguarnera L, Cristaldi E, Malaguarnera M. The role of immunity in elderly cancer. *Crit Rev Oncol Hematol*. 2010;74(1):40–60.
- Müller L, Fulop T, Pawelec G. Immunosenescence in vertebrates and invertebrates. *Immun Ageing I & A*. 2013;10(1):12.
- Qi Q, Liu Y, Cheng Y, Glanville J, Zhang D, Lee JY, et al. Diversity and clonal selection in the human T-cell repertoire. *Proc Natl Acad Sci U S A*. 2014;111(36):13139–44.
- Qi Q, Zhang DW, Weyand CM, Goronzy JJ. Mechanisms shaping the naive T cell repertoire in the elderly – Thymic involution or peripheral homeostatic proliferation? *Exp Gerontol*. 2014;54:71–4.
- Vescovini R, Fagnoni FF, Telera AR, Bucci L, Pedrazzoni M, Magalini F, et al. Naive and memory

- CD8 T cell pool homeostasis in advanced aging: impact of age and of antigen-specific responses to cytomegalovirus. *Age (Dordr)*. 2014;36(2):625–40.
28. Wistuba-Hamprecht K, Haehnel K, Janssen N, Demuth I, Pawelec G. Peripheral blood T-cell signatures from high-resolution immune phenotyping of gammadelta and alphabeta T-cells in younger and older subjects in the Berlin Aging Study II. *Immun Ageing I & A*. 2015;12:25.
 29. Johnson PL, Goronzy JJ, Antia R. A population biological approach to understanding the maintenance and loss of the T-cell repertoire during aging. *Immunology*. 2014;142(2):167–75.
 30. Naylor K, Li G, Vallejo AN, Lee WW, Koetz K, Bryl E, et al. The influence of age on T cell generation and TCR diversity. *J Immunol*. 2005;174(11):7446–52.
 31. Salam N, Rane S, Das R, Faulkner M, Gund R, Kandpal U, et al. T cell ageing: effects of age on development, survival & function. *Indian J Med Res*. 2013;138(5):595–608.
 32. Arnold CR, Wolf J, Brunner S, Herndler-Brandstetter D, Grubeck-Loebenstern B. Gain and loss of T cell subsets in old age—age-related reshaping of the T cell repertoire. *J Clin Immunol*. 2011;31(2):137–46.
 33. Geiger H, de Haan G, Florian MC. The ageing haematopoietic stem cell compartment. *Nat Rev Immunol*. 2013;13(5):376–89.
 34. Compston JE. Bone marrow and bone: a functional unit. *J Endocrinol*. 2002;173(3):387–94.
 35. Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. *J Pathol*. 2007;211(2):144–56.
 36. Warren LA, Rossi DJ. Stem cells and aging in the hematopoietic system. *Mech Ageing Dev*. 2009;130(1–2):46–53.
 37. Beerman I, Maloney WJ, Weissmann IL, Rossi DJ. Stem cells and the aging hematopoietic system. *Curr Opin Immunol*. 2010;22(4):500–6.
 38. Gui J, Zhu X, Dohkan J, Cheng L, Barnes PF, Su DM. The aged thymus shows normal recruitment of lymphohematopoietic progenitors but has defects in thymic epithelial cells. *Int Immunol*. 2007;19(10):1201–11.
 39. Palmer DB. The effect of age on thymic function. *Front Immunol*. 2013;4:316.
 40. Anderson G, Jenkinson EJ. Lymphostromal interactions in thymic development and function. *Nat Rev Immunol*. 2001;1(1):31–40.
 41. Poulin JF, Viswanathan MN, Harris JM, Komanduri KV, Wieder E, Ringuette N, et al. Direct evidence for thymic function in adult humans. *J Exp Med*. 1999;190(4):479–86.
 42. Nikolich-Zugich J, Li G, Uhrhlab JL, Renkema KR, Smithy MJ. Age-related changes in CD8 T cell homeostasis and immunity to infection. *Semin Immunol*. 2012;24(5):356–64.
 43. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014;69(Suppl 1):S4–9.
 44. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908:244–54.
 45. Bennett JM, Glaser R, Malarkey WB, Beversdorf DQ, Peng J, Kiecolt-Glaser JK. Inflammation and reactivation of latent herpesviruses in older adults. *Brain Behav Immun*. 2012;26(5):739–46.
 46. Pawelec G, Derhovanessian E. Role of CMV in immune senescence. *Virus Res*. 2011;157(2):175–9.
 47. Pawelec G, Larbi A, Derhovanessian E. Senescence of the human immune system. *J Comp Pathol*. 2010;142(Suppl 1):S39–44.
 48. Tsaknaridis L, Spencer L, Culbertson N, Hicks K, LaTocha D, Chou YK, et al. Functional assay for human CD4+CD25+ Treg cells reveals an age-dependent loss of suppressive activity. *J Neurosci Res*. 2003;74(2):296–308.
 49. Fessler J, Ficjan A, Duftner C, Dejaco C. The impact of aging on regulatory T-cells. *Front Immunol*. 2013;4:231.
 50. Pawelec G, Schneider EM, Wernet P. Acquisition of suppressive activity and natural killer-like cytotoxicity by human alloproliferative “helper” T cell clones. *J Immunol*. 1986;136(2):402–11.
 51. Jagger A, Shimojima Y, Goronzy JJ, Weyand CM. Regulatory T cells and the immune aging process: a mini-review. *Gerontology*. 2014;60(2):130–7.
 52. Vadasz Z, Haj T, Kessel A, Toubi E. Age-related autoimmunity. *BMC Med*. 2013;11:94.
 53. Singh T, Newman AB. Inflammatory markers in population studies of aging. *Ageing Res Rev*. 2011;10(3):319–29.
 54. Rodier F, Campisi J. Four faces of cellular senescence. *J Cell Biol*. 2011;192(4):547–56.
 55. Coppe JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol*. 2010;5:99–118.
 56. Pawelec G. T-cell immunity in the aging human. *Haematologica*. 2014;99(5):795–7.
 57. Tchkonja T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J Clin Invest*. 2013;123(3):966–72.
 58. Larbi A, Fulop T, Pawelec G. Immune receptor signaling, aging and autoimmunity. *Adv Exp Med Biol*. 2008;640:312–24.
 59. Fulop T, Larbi A, Pawelec G. Human T cell aging and the impact of persistent viral infections. *Front Immunol*. 2013;4:271.
 60. Hohensinner PJ, Goronzy JJ, Weyand CM. Telomere dysfunction, autoimmunity and aging. *Ageing Dis*. 2011;2(6):524–37.
 61. Hearps AC, Martin GE, Angelovich TA, Cheng WJ, Maisa A, Landay AL, et al. Aging is associated with chronic innate immune activation and dysregulation of monocyte phenotype and function. *Ageing Cell*. 2012;11(5):867–75.
 62. de Pablo-Bernal RS, Canizares J, Rosado I, Galva MI, Alvarez-Rios AI, Carrillo-Vico A, et al.

- Monocyte phenotype and polyfunctionality are associated with elevated soluble inflammatory markers, cytomegalovirus infection, and functional and cognitive decline in elderly adults. *J Gerontol A Biol Sci Med Sci*. 2016;71(5):610–8.
63. Di Benedetto S, Wistuba-Hamprecht K, Goldeck D, Öttinger L, Demuth I, Pawelec G, et al. The modulatory effect of age, gender and Cytomegalovirus (CMV) persistence on peripheral blood immune cell subsets in participants of the Berlin Aging Study II. *Psychophysiology*. 2017;54(S1):86.
 64. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev*. 2007;128(1):92–105.
 65. Di Benedetto S, Müller L, Wenger E, Duzel S, Pawelec G. Contribution of neuroinflammation and immunity to brain aging and the mitigating effects of physical and cognitive interventions. *Neurosci Biobehav Rev*. 2017;75:114–28.
 66. Giunta B, Fernandez F, Nikolich WV, Obregon D, Rrapo E, Town T, et al. Inflammaging as a prodrome to Alzheimer's disease. *J Neuroinflammation*. 2008;5:51.
 67. von Bernhardi R, Tichauer JE, Eugenin J. Aging-dependent changes of microglial cells and their relevance for neurodegenerative disorders. *J Neurochem*. 2010;112(5):1099–114.
 68. Pizza V, Agresta A, D'Acunto CW, Festa M, Capasso A. Neuroinflammation and ageing: current theories and an overview of the data. *Rev Recent Clin Trials*. 2011;6(3):189–203.
 69. Harrisson NA. Brain structures implicated in inflammation-associated depression. *Curr Top Behav Neurosci*. 2016;31:221–48.
 70. Goldeck D, Witkowski JM, Fulop T, Pawelec G. Peripheral immune signatures in Alzheimer disease. *Curr Alzheimer Res*. 2016;13(7):739–49.
 71. Ownby RL. Neuroinflammation and cognitive aging. *Curr Psychiatry Rep*. 2010;12(1):39–45.
 72. Barrientos RM, Kitt MM, Watkins LR, Maier SF. Neuroinflammation in the normal aging hippocampus. *Neuroscience*. 2015;309:84–99.
 73. Barrientos RM, Frank MG, Watkins LR, Maier SF. Aging-related changes in neuroimmune-endocrine function: implications for hippocampal-dependent cognition. *Horm Behav*. 2012;62(3):219–27.
 74. Capoccia S, Berry A, Bellisario V, Vacirca D, Ortona E, Alleva E, et al. Quality and timing of stressors differentially impact on brain plasticity and neuroendocrine-immune function in mice. *Neural Plast*. 2013;2013:971817.
 75. Hansel A, Hong S, Camara RJ, von Kanel R. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. *Neurosci Biobehav Rev*. 2010;35(1):115–21.
 76. Bisht K, Sharma KP, Lecours C, Sanchez MG, El Hajj H, Milior G, et al. Dark microglia: a new phenotype predominantly associated with pathological states. *Glia*. 2016;64(5):826–39.
 77. Tay TL, Savage J, Hui CW, Bisht K, Tremblay ME. Microglia across the lifespan: from origin to function in brain development, plasticity and cognition. *J Physiol*. 2016;595(6):1929–45.
 78. Sparkman NL, Johnson RW. Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. *Neuroimmunomodulation*. 2008;15(4–6):323–30.
 79. Norden DM, Muccigrosso MM, Godbout JP. Microglial priming and enhanced reactivity to secondary insult in aging, and traumatic CNS injury, and neurodegenerative disease. *Neuropharmacology*. 2015;96(Pt A):29–41.
 80. Doty KR, Guillot-Sestier MV, Town T. The role of the immune system in neurodegenerative disorders: adaptive or maladaptive? *Brain Res*. 2015;1617:155–73.
 81. Deleidi M, Jaggle M, Rubino G. Immune aging, dysmetabolism, and inflammation in neurological diseases. *Front Neurosci*. 2015;9:172.
 82. Gemechu JM, Bentivoglio M. T cell recruitment in the brain during normal aging. *Front Cell Neurosci*. 2012;6:38.
 83. Campbell A. Inflammation, neurodegenerative diseases, and environmental exposures. *Ann NY Acad Sci*. 2004;1035:117–32.
 84. Chen WW, Zhang X, Huang WJ. Role of neuroinflammation in neurodegenerative diseases (review). *Mol Med Rep*. 2016;13(4):3391–6.
 85. Leza JC, Garcia-Bueno B, Bioque M, Arango C, Parellada M, Do K, et al. Inflammation in schizophrenia: a question of balance. *Neurosci Biobehav Rev*. 2015;55:612–26.
 86. Corbi G, Conti V, Davinelli S, Scapagnini G, Filippelli A, Ferrara N. Dietary phytochemicals in neuroimmunoaging: a new therapeutic possibility for humans? *Front Pharmacol*. 2016;7:364.
 87. Anderson RM, Weindruch R. The caloric restriction paradigm: implications for healthy human aging. *Am J Human Biol*. 2012;24(2):101–6.
 88. Nikolich-Zugich J, Messaoudi I. Mice and flies and monkeys too: caloric restriction rejuvenates the aging immune system of non-human primates. *Exp Gerontol*. 2005;40(11):884–93.
 89. Jolly CA. Is dietary restriction beneficial for human health, such as for immune function? *Curr Opin Lipidol*. 2007;18(1):53–7.
 90. Goldberg EL, Romero-Aleshire MJ, Renkema KR, Ventevogel MS, Chew WM, Uhrlaub JL, et al. Lifespan-extending caloric restriction or mTOR inhibition impair adaptive immunity of old mice by distinct mechanisms. *Aging Cell*. 2015;14(1):130–8.
 91. Meydani SN, Das SK, Pieper CF, Lewis MR, Klein S, Dixit VD, et al. Long-term moderate calorie restriction inhibits inflammation without impairing cell-mediated immunity: a randomized controlled trial in non-obese humans. *Aging (Albany NY)*. 2016;8(7):1416–31.
 92. Guigoz Y, Dore J, Schiffrin EJ. The inflammatory status of old age can be nurtured from the intesti-

- nal environment. *Curr Opin Clin Nutr Metab Care*. 2008;11(1):13–20.
93. Biagi E, Candela M, Fairweather-Tait S, Franceschi C, Brigidi P. Aging of the human metaorganism: the microbial counterpart. *Age*. 2012;34(1):247–67.
 94. Biagi E, Nylund L, Candela M, Ostan R, Bucci L, Pini E, et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. *PLoS One*. 2010;5(5):e10667.
 95. Blum S, Haller D, Pfeifer A, Schiffrin EJ. Probiotics and immune response. *Clin Rev Allergy Immunol*. 2002;22(3):287–309.
 96. Meydani SN, Ha WK. Immunologic effects of yogurt. *Am J Clin Nutr*. 2000;71(4):861–72.
 97. Takeda K, Okumura K. Effects of a fermented milk drink containing *Lactobacillus casei* strain Shirota on the human NK-cell activity. *J Nutr*. 2007;137(3 Suppl 2):791S–3S.
 98. Schiffrin EJ, Morley JE, Donnet-Hughes A, Guigoz Y. The inflammatory status of the elderly: the intestinal contribution. *Mutat Res*. 2010;690(1–2):50–6.
 99. Vulevic J, Drakoularakou A, Yaqoob P, Tzortzis G, Gibson GR. Modulation of the fecal microflora profile and immune function by a novel trans-galactooligosaccharide mixture (B-GOS) in healthy elderly volunteers. *Am J Clin Nutr*. 2008;88(5):1438–46.
 100. Boge T, Remigy M, Vaudaine S, Tanguy J, Bourdet-Sicard R, van der Werf S. A probiotic fermented dairy drink improves antibody response to influenza vaccination in the elderly in two randomised controlled trials. *Vaccine*. 2009;27(41):5677–84.
 101. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine*. 2006;24(8):1159–69.
 102. Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, et al. Treg induction by a rationally selected mixture of *Clostridia* strains from the human microbiota. *Nature*. 2013;500(7461):232–6.
 103. Adzersen KH, Jess P, Freivogel KW, Gerhard I, Bastert G. Raw and cooked vegetables, fruits, selected micronutrients, and breast cancer risk: a case-control study in Germany. *Nutr Cancer*. 2003;46(2):131–7.
 104. Ames BN, Wakimoto P. Are vitamin and mineral deficiencies a major cancer risk? *Nat Rev Cancer*. 2002;2(9):694–704.
 105. Chadalapaka G, Jutooru I, McAlees A, Stefanac T, Safe S. Structure-dependent inhibition of bladder and pancreatic cancer cell growth by 2-substituted glycyrrhetic and ursolic acid derivatives. *Bioorg Med Chem Lett*. 2008;18(8):2633–9.
 106. Kwak JH, Lee JH, Ahn CW, Park SH, Shim ST, Song YD, et al. Black soy peptide supplementation improves glucose control in subjects with prediabetes and newly diagnosed type 2 diabetes mellitus. *J Med Food*. 2010;13(6):1307–12.
 107. Prasad S, Sung B, Aggarwal BB. Age-associated chronic diseases require age-old medicine: role of chronic inflammation. *Prev Med*. 2012;54(Suppl):S29–37.
 108. Zhang YX, Kong CZ, Wang LH, Li JY, Liu XK, Xu B, et al. Ursolic acid overcomes Bcl-2-mediated resistance to apoptosis in prostate cancer cells involving activation of JNK-induced Bcl-2 phosphorylation and degradation. *J Cell Biochem*. 2010;109(4):764–73.
 109. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. *Biochem Pharmacol*. 2006;71(10):1397–421.
 110. Sears B. Anti-inflammatory diets. *J Am Coll Nutr*. 2015;34(Suppl 1):14–21.
 111. Essa MM, Vijayan RK, Castellano-Gonzalez G, Memon MA, Braidy N, Guillemin GJ. Neuroprotective effect of natural products against Alzheimer's disease. *Neurochem Res*. 2012;37(9):1829–42.
 112. Pae M, Wu D. Nutritional modulation of age-related changes in the immune system and risk of infection. *Nutr Res*. 2017;41:14–35.
 113. Panickar KS, Jewell DE. The beneficial role of anti-inflammatory dietary ingredients in attenuating markers of chronic low-grade inflammation in aging. *Horm Mol Biol Clin Investig*. 2015;23(2):59–70.
 114. Pennisi M, Crupi R, Di Paola R, Ontario ML, Bella R, Calabrese EJ, et al. Inflammasomes, hormones, and antioxidants in neuroinflammation: role of NRLP3 in Alzheimer disease. *J Neurosci Res*. 2017;95(7):1360–72.
 115. Perez SD, Du K, Rendeiro C, Wang L, Wu Q, Rubakhin SS, et al. A unique combination of micronutrients rejuvenates cognitive performance in aged mice. *Behav Brain Res*. 2017;320:97–112.
 116. Ricordi C, Garcia-Contreras M, Farnetti S. Diet and inflammation: possible effects on immunity, chronic diseases, and life span. *J Am Coll Nutr*. 2015;34(Suppl 1):10–3.
 117. Zhang Q, Yuan L, Zhang Q, Gao Y, Liu G, Xiu M, et al. Resveratrol attenuates hypoxia-induced neurotoxicity through inhibiting microglial activation. *Int Immunopharmacol*. 2015;28(1):578–87.
 118. Essa MM, Subash S, Akbar M, Al-Adawi S, Guillemin GJ. Long-term dietary supplementation of pomegranates, figs and dates alleviate neuroinflammation in a transgenic mouse model of Alzheimer's disease. *PLoS One*. 2015;10(3):e0120964.
 119. Barnett JB, Dao MC, Hamer DH, Kandel R, Brandeis G, Wu D, et al. Effect of zinc supplementation on serum zinc concentration and T cell proliferation in nursing home elderly: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2016;103(3):942–51.
 120. Sheikh A, Shamsuzzaman S, Ahmad SM, Nasrin D, Nahar S, Alam MM, et al. Zinc influences innate immune responses in children with enterotoxigenic *Escherichia coli*-induced diarrhea. *J Nutr*. 2010;140(5):1049–56.
 121. Monacelli F, Acquarone E, Giannotti C, Borghi R, Nencioni A. Vitamin C, aging and Alzheimer's disease. *Nutrients*. 2017;9(7):1–26.
 122. Meydani SN, Barklund MP, Liu S, Meydani M, Miller RA, Cannon JG, et al. Vitamin E supplement

- tation enhances cell-mediated immunity in healthy elderly subjects. *Am J Clin Nutr.* 1990;52(3):557–63.
123. Molano A, Meydani SN. Vitamin E, signalosomes and gene expression in T cells. *Mol Asp Med.* 2012;33(1):55–62.
124. Wu D, Meydani SN. Age-associated changes in immune function: impact of vitamin E intervention and the underlying mechanisms. *Endocr Metab Immune Disord Drug Targets.* 2014;14(4):283–9.
125. Kim SS, Oh OJ, Min HY, Park EJ, Kim Y, Park HJ, et al. Eugenol suppresses cyclooxygenase-2 expression in lipopolysaccharide-stimulated mouse macrophage RAW264.7 cells. *Life Sci.* 2003;73(3):337–48.
126. Tripathi S, Maier KG, Bruch D, Kittur DS. Effect of 6-gingerol on pro-inflammatory cytokine production and costimulatory molecule expression in murine peritoneal macrophages. *J Surg Res.* 2007;138(2):209–13.
127. Shishodia S, Potdar P, Gairola CG, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates cigarette smoke-induced NF-kappaB activation through inhibition of IkappaBalpha kinase in human lung epithelial cells: correlation with suppression of COX-2, MMP-9 and cyclin D1. *Carcinogenesis.* 2003;24(7):1269–79.
128. Chainy GB, Manna SK, Chaturvedi MM, Aggarwal BB. Anethole blocks both early and late cellular responses transduced by tumor necrosis factor: effect on NF-kappaB, AP-1, JNK, MAPKK and apoptosis. *Oncogene.* 2000;19(25):2943–50.
129. Kim DH, Kim CH, Kim MS, Kim JY, Jung KJ, Chung JH, et al. Suppression of age-related inflammatory NF-kappaB activation by cinnamaldehyde. *Biogerontology.* 2007;8(5):545–54.
130. Andersson D, Liu JJ, Nilsson A, Duan RD. Ursolic acid inhibits proliferation and stimulates apoptosis in HT29 cells following activation of alkaline sphingomyelinase. *Anticancer Res.* 2003;23(4):3317–22.
131. Es-saady D, Simon A, Ollier M, Maurizis JC, Chulia AJ, Delage C. Inhibitory effect of ursolic acid on B16 proliferation through cell cycle arrest. *Cancer Lett.* 1996;106(2):193–7.
132. Hsu YL, Kuo PL, Lin CC. Proliferative inhibition, cell-cycle dysregulation, and induction of apoptosis by ursolic acid in human non-small cell lung cancer A549 cells. *Life Sci.* 2004;75(19):2303–16.
133. Harmand PO, Duval R, Delage C, Simon A. Ursolic acid induces apoptosis through mitochondrial intrinsic pathway and caspase-3 activation in M4Beu melanoma cells. *Int J Cancer (Journal International du Cancer).* 2005;114(1):1–11.
134. Pathak AK, Bhutani M, Nair AS, Ahn KS, Chakraborty A, Kadara H, et al. Ursolic acid inhibits STAT3 activation pathway leading to suppression of proliferation and chemosensitization of human multiple myeloma cells. *Mol Cancer Res (MCR).* 2007;5(9):943–55.
135. Yim EK, Lee KH, Namkoong SE, Um SJ, Park JS. Proteomic analysis of ursolic acid-induced apoptosis in cervical carcinoma cells. *Cancer Lett.* 2006;235(2):209–20.
136. Almeida S, Alves MG, Sousa M, Oliveira PF, Silva BM. Are polyphenols strong dietary agents against neurotoxicity and neurodegeneration? *Neurotox Res.* 2016;30(3):345–66.
137. Wu Z, Yu J, Zhu A, Nakanishi H. Nutrients, microglia aging, and brain aging. *Oxidative Med Cell Longev.* 2016;2016:7498528.
138. Wiesmann M, Zerbi V, Jansen D, Haast R, Lutjohann D, Broersen LM, et al. A dietary treatment improves cerebral blood flow and brain connectivity in aging apoE4 mice. *Neural Plast.* 2016;2016:6846721.
139. Jang S, Kelley KW, Johnson RW. Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1. *Proc Natl Acad Sci U S A.* 2008;105(21):7534–9.
140. Burton MD, Ryttych JL, Amin R, Johnson RW. Dietary luteolin reduces proinflammatory microglia in the brain of senescent mice. *Rejuvenation Res.* 2016;19(4):286–92.
141. Szwajgier D, Borowiec K, Pustelniak K. The Neuroprotective effects of phenolic acids: molecular mechanism of action. *Nutrients.* 2017;9(5):1–21.
142. Mohammadzadeh Honarvar N, Saedisomeolia A, Abdolahi M, Shayeganrad A, Taheri Sangsari G, Hassanzadeh Rad B, et al. Molecular anti-inflammatory mechanisms of retinoids and carotenoids in Alzheimer's disease: a review of current evidence. *J Mol Neurosci.* 2017;61(3):289–304.
143. Liu Z, Chen Y, Qiao Q, Sun Y, Liu Q, Ren B, et al. Sesamol supplementation prevents systemic inflammation-induced memory impairment and amyloidogenesis via inhibition of nuclear factor kappaB. *Mol Nutr Food Res.* 2017;61(5):237–47.
144. Vauzour D, Camprubi-Robles M, Miquel-Kergoat S, Andres-Lacueva C, Banati D, Barberger-Gateau P, et al. Nutrition for the ageing brain: towards evidence for an optimal diet. *Ageing Res Rev.* 2017;35:222–40.
145. Vauzour D, Martinsen A, Laye S. Neuroinflammatory processes in cognitive disorders: is there a role for flavonoids and n-3 polyunsaturated fatty acids in counteracting their detrimental effects? *Neurochem Int.* 2015;89:63–74.
146. Molfino A, Gioia G, Rossi Fanelli F, Muscaritoli M. The role for dietary omega-3 fatty acids supplementation in older adults. *Nutrients.* 2014;6(10):4058–73.
147. Devassy JG, Leng S, Gabbs M, Monirujjaman M, Aukema HM. Omega-3 polyunsaturated fatty acids and oxylipins in neuroinflammation and management of Alzheimer disease. *Adv Nutr.* 2016;7(5):905–16.
148. Dong Y, Xu M, Kalueff AV, Song C. Dietary eicosapentaenoic acid normalizes hippocampal omega-3 and 6 polyunsaturated fatty acid profile, attenuates glial activation and regulates BDNF function in a rodent model of neuroinflammation induced by

- central interleukin-1beta administration. *Eur J Nutr.* 2017;57(5):1781–91.
149. Sun GY, Simonyi A, Fritsche KL, Chuang DY, Hannink M, Gu Z, et al. Docosahexaenoic acid (DHA): an essential nutrient and a nutraceutical for brain health and diseases. *Prostaglandins Leukot Essent Fatty Acids.* 2017;136:3–13.
 150. Carvalho A, Rea IM, Parimon T, Cusack BJ. Physical activity and cognitive function in individuals over 60 years of age: a systematic review. *Clin Interv Aging.* 2014;9:661–82.
 151. Kirk-Sanchez NJ, McGough EL. Physical exercise and cognitive performance in the elderly: current perspectives. *Clin Interv Aging.* 2014;9:51–62.
 152. Moylan S, Eyre HA, Maes M, Baune BT, Jacka FN, Berk M. Exercising the worry away: how inflammation, oxidative and nitrogen stress mediates the beneficial effect of physical activity on anxiety disorder symptoms and behaviours. *Neurosci Biobehav Rev.* 2013;37(4):573–84.
 153. Barrientos RM, Frank MG, Crysedale NY, Chapman TR, Ahrendsen JT, Day HE, et al. Little exercise, big effects: reversing aging and infection-induced memory deficits, and underlying processes. *J Neurosci.* 2011;31(32):11578–86.
 154. Kohman RA, DeYoung EK, Bhattacharya TK, Peterson LN, Rhodes JS. Wheel running attenuates microglia proliferation and increases expression of a proneurogenic phenotype in the hippocampus of aged mice. *Brain Behav Immun.* 2012;26(5):803–10.
 155. Majka DS, Chang RW, Vu TH, Palmas W, Geffken DF, Ouyang P, et al. Physical activity and high-sensitivity C-reactive protein in the multi-ethnic study of atherosclerosis. *Am J Prev Med.* 2009;36(1):56–62.
 156. Pedersen BK. Exercise-induced myokines and their role in chronic diseases. *Brain Behav Immun.* 2011;25(5):811–6.
 157. Timmerman KL, Flynn MG, Coen PM, Markofski MM, Pence BD. Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? *J Leukoc Biol.* 2008;84(5):1271–8.
 158. Dishman RK, Berthoud HR, Booth FW, Cotman CW, Edgerton VR, Fleshner MR, et al. Neurobiology of exercise. *Obesity.* 2006;14(3):345–56.
 159. Minter MR, Moore Z, Zhang M, Brody KM, Jones NC, Shultz SR, et al. Deletion of the type-1 interferon receptor in APPSWE/PS1DeltaE9 mice preserves cognitive function and alters glial phenotype. *Acta Neuropathol Commun.* 2016;4(1):72.
 160. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. *Physiol Rev.* 2000;80(3):1055–81.
 161. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol (1985).* 2005;98(4):1154–62.
 162. Phillips C, Baktir MA, Srivatsan M, Salehi A. Neuroprotective effects of physical activity on the brain: a closer look at trophic factor signaling. *Front Cell Neurosci.* 2014;8:170.
 163. Simpson RJ. Aging and inflammation: directing traffic through physical activity. *Brain Behav Immun.* 2016;56:10–1.
 164. Kohut ML, Senchina DS. Reversing age-associated immunosenescence via exercise. *Exerc Immunol Rev.* 2004;10:6–41.
 165. Vaupel JW, Carey JR, Christensen K. Aging. It's never too late. *Science.* 2003;301(5640):1679–81.
 166. Lindenberger U. Human cognitive aging: corriger la fortune? *Science.* 2014;346(6209):572–8.
 167. Tolppanen AM, Solomon A, Kulmala J, Kareholt I, Ngandu T, Rusanen M, et al. Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. *Alzheimers Dement.* 2015;11(4):434–43 e6.
 168. Mijanur Rahman M, Gan SH, Khalil MI. Neurological effects of honey: current and future prospects. *Evid Based Complement Alternat Med.* 2014;2014:958721.
 169. Kurtys E, Eisel UL, Verkuyll JM, Broersen LM, Dierckx RA, de Vries EF. The combination of vitamins and omega-3 fatty acids has an enhanced anti-inflammatory effect on microglia. *Neurochem Int.* 2016;99:206–14.
 170. Vauzour D. Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. *Oxidative Med Cell Longev.* 2012;2012:914273.